Review Article

Advances in the diagnosis and treatment of gastric neuroendocrine neoplasms

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Abstract: Gastric neuroendocrine neoplasms (g-NENs) are a group of heterogeneous tumors arising from the endocrine cells of stomach. Most g-NENs progresses slowly and have a long disease course; however, some other g-NENs grow rapidly, similar to the progression of gastric adenocarcinoma. g-NENs have complex and diverse clinical manifestations and their prognosis and treatment strategies depend highly on clinical subtype, pathological grade, tumour stage, and other factors. Due to their low prevalence, most clinicians have limited knowledge about g-NENs. Missed diagnosis and excessive/inadequate treatment is common in clinical settings. Thus, the diagnosis and treatment of g-NENs needs to be further standardized.

Keywords: Gastric neuroendocrine neoplasms; g-NENs

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Epidemiology

According to the United States Surveillance, Epidemiology, and End Results (SEER) database, gastric neuroendocrine neoplasms (g-NENs) accounted for 2.2% among all NENs for the period from 1950 to 1969 and up to 6% for the period from 2000 to 2007 (1). The increasing prevalence of g-NENs may be explained by the wider application of gastroscopy, which contributes to the early diagnosis. A prospective study in Austria collected a total of 285 cases of gastrointestinal neuroendocrine tumors from May 2004 to April 2005, yielding an annual incidence of 2.39/100,000, among which g-NENs accounted for 23% of all gastrointestinal neuroendocrine tumors (2). A prospective study in the Republic of Korea collected a total of 4,951 cases of gastrointestinal neuroendocrine tumors from 2000 to 2009, among which g-NENs accounted for 14.6%; stomach was the second most commonly affected site (second only to rectum) (3). A research in Argentina indicated that g-NENs accounted for 6.9% of all gastrointestinal NENs (4). Currently no epidemiological data on g-NENs based on multicenter prospective studies have been available in China.

Pathological diagnostic criteria

Besides gastroscopic observation with the naked eye, histopathology is essential for the diagnosis of g-NENs. According to the World Health Organization grading criteria of gastroenteropancreatic neuroendocrine tumors (5), NETs can be divided into NET G1, NET G2, NEC G3, and MANEC. In recent years, it has been found that in some patients the tumors may be well-differentiated but the Ki-67 reached G3 (exceeding 20%, although typically not exceeding 60%). Such tumors could not be classified according to the current WHO classification system. In 2013, a Chinese pathologist panel published a consensus document, in which this condition was named as “highly proliferative NETs”, with an attempt to distinguish it from NET G3. *Table 1* is the World Health Organization grading criteria of gastroenteropancreatic neuroendocrine tumors [2010].

Tumor stage

Stage is a key prognostic factor for tumors. g-NENs are no exception. The TNM staging system was initially published

Table 1 The World Health Organization grading criteria of gastroenteropancreatic neuroendocrine tumors [2010]

Grade	Mitotic figures (/10 HPF)	Ki-67 index (% positive)
G1	<2	2
G2	2–20	3–20
G3	>20	>20

by the European Neuroendocrine Tumor Society (ENETS) in 2006. Later the American Joint Committee on Cancer (AJCC) staging system also describes the TNM of g-NENs. However, definition of T stage is slightly different between these two staging systems (*Table 2*). There is no final conclusion which of these two stage systems is better. The specific staging system used in a clinical trial must be clearly stated.

Clinical typing

In addition to pathological typing and tumor staging, the clinical typing of g-NENs is also very important. Different g-NEN types have dramatically different prognosis and treatment strategies. Classification systems distinguishing three or four types of gastric carcinoid tumor have been proposed: the former divides the well-differentiated g-NENs into three types (8,9): type 1 (tumors associated with chronic atrophic gastritis), type 2 (tumors associated with gastrinoma/MEN-1), and type 3 (sporadic lesions). Patients with type 1 or type 2 g-NEN typically have hypergastrinemia; however, type 1 patients have achlorhydria, whereas type 2 patients suffer from excessive gastric acid secretion. Type 3 patients have normal gastrin level and normal gastric acid secretion. The four-type classification, based on the three-type classification, classifies the poorly-differentiated g-NEN and MANEC into type 4 (10-14). We believe the four-type classification is more practical and covers all the g-NENs. The clinicopathological features of each g-NEN type are summarized in *Table 3*.

Diagnosis

Gastroscopy and biopsy

Careful assessment of the tumor and its background mucosa using gastroscopy is particularly important for the typing of g-NENs. Multiple specimens were collected from the tumor, and two or more mucosal specimens were obtained from gastric fundus, gastric body, and gastric antrum (15). For tumors larger than 1 cm, endoscopic ultrasonography is recommended to identify the depth of tumor invasion into the gastric wall and the possible involvement of surrounding lymph nodes.

Pathology

The pathological diagnosis of g-NENs may follow the criteria proposed in the Concensus on the Pathological Diagnosis of Gastroenteropancreatic Neuroendocrine Tumors in China (2013 edition) (16), with the essential immunohistochemical items including CgA, Syn, and Ki-67. In patients with type 1 g-NEN, the microscopic findings may include fundal atrophic gastritis, proliferation of neuroendocrine cells, and antral G-cell hyperplasia (17).

Serum gastrin and CgA

Serum gastrin is a key indicator for clinical typing and an essential test item for g-NENs. Elevated serum gastrin can be seen in patients with type 1 or type 2 g-NENs; in contrast, the serum gastrin level can be normal in type 3 well-differentiated g-NEN. Serum CgA has certain role in the auxiliary diagnosis and disease monitoring of patients with g-NENs. NSE may increase in poorly-differentiated neuroendocrine carcinoma (type 4).

Twenty four-hour gastric pH monitoring

Twenty four-hour gastric pH monitoring may be considered in patient with elevated serum gastrin (18). Patients with type 1 g-NEN have achlorhydria (pH >4), whereas those with type 2 g-NEN suffer from excessive gastric acid secretion (pH <2). The gastric secretion is normal in type 3 patients (pH <4).

Other laboratory tests

In patients suspicious for type 1 g-NEN, the levels of gastric parietal cell antibody, intrinsic factor antibodies, serum vitamin B_{12}, and thyroid function and antibodies may be detected. The gastric parietal cell antibody is positive in about 80% of type 1 g-NEN patients, whereas some patients may also have serum vitamin B_{12} deficiency and/

Table 2 Definition of T stage and staging system for g-NENs in the ENETS and AJCC systems

ENETS TNM staging system (6)				AJCC TNM staging system (7)			
T—primary tumor				Primary tumor (T)			
TX	Primary tumor cannot be assessed			TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor			T0	No evidence of primary tumor		
Tis	*In situ* tumor/dysplasia (<0.5 mm)			Tis	Carcinoma *in situ*/dysplasia (tumor size <0.5 mm), confined to mucosa		
T1	Tumor invades lamina propria or submucosa and ≤1 cm			T1	Tumor invades lamina propria or submucosa and ≤1 cm in size		
T2	Tumor invades muscularis propria or subserosa or >1 cm			T2	Tumor invades muscularis propria or >1 cm in size		
T3	Tumor penetrates serosa			T3	Tumor penetrates subserosa		
T4	Tumor invades adjacent structures			T4	Tumor invades visceral peritoneum (serosal) or other organs or adjacent structures		
For any T, add (m) for multiple tumors				For any T, add (m) for multiple tumors			
N—regional lymph nodes				Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed			NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis			N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis			N1	Regional lymph node metastasis		
M—distant metastasis				Distant metastases (M)			
MX	Distant metastasis cannot be assessed			–	–		
M0	No distant metastases			M0	No distant metastases		
M1	Distant metastasis			M1	Distant metastasis		
Stage				Stage			
Stage 0	Tis	N0	M0	Stage 0	Tis	N0	M0
Stage I	T1	N0	M0	Stage I	T1	N0	M0
Stage IIa	T2	N0	M0	Stage IIA	T2	N0	M0
Stage IIb	T3	N0	M0	Stage IIB	T3	N0	M0
Stage IIIa	T4	N0	M0	Stage IIIA	T4	N0	M0
Stage IIIb	Any T	N1	M0	Stage IIIB	Any T	N1	M0
Stage IV	Any T	Any N	M1	Stage IV	Any T	Any N	M1

g-NENs, gastric neuroendocrine neoplasms; ENETS, European Neuroendocrine Tumor Society; AJCC, American Joint Committee on Cancer.

or anemia. Some type 1 g-NEN patients may also have autoimmune thyroiditis. In patients suspicious for type 2 g-NEN, the blood pituitary hormones, parathyroid hormone, and calcium (in addition to serum gastrin) should also be measured to rule out the possibility of MEN-1.

Routine imaging

The type 1 gastric NET has good prognosis and rarely results in metastasis. For the other three types, thoracic/abdominal contrast-enhanced CT or MRI should be performed to identify any lymph node involvement or

Table 3 Different types of g-NENs and their clinicopathological features (13)

Main characteristics	Type 1	Type 2	Type 3	Type 4
Proportion (%)	70–80	5–6	14–25	Rare
Associated disease	Type A atrophic gastritis	Gastrinoma/MEN-1	None	None
Site of the tumor	Gastric fundus/body	Gastric fundus/body	Any site	Any site
Serum gastrin	Elevated	Elevated	Normal	Mostly normal
Gastric acid secretion	Deficient	Increased	Normal	Mostly normal
Number of tumor	Multiple	Multiple	Solitary	Solitary
Tumor size	<1–2 cm	<1–2 cm	Mostly >2 cm	>2 cm
Pathology	Mostly NET G1	NET G1/G2	NET G1/G2/G3	NEC G3 or MANEC
Prognosis	Good	Fair	Poor	Extremely poor

distant metastasis. In patients suspicious for type 2 g-NEN, corresponding imaging should be performed to locate the g-NENs and rule out the possibility of MEN-1.

Nuclear medicine examinations

Nuclear medicine examinations include somatostatin receptor scintigraphy (SRS), ^{68}Ga-DOTANOC PET/CT, and ^{18}F-FDG PET/CT. Both SRS and ^{68}Ga-DOTANOC PET/CT can be used for well-differentiated NENs (the latter is even more sensitive). In contrast, ^{18}F-FDG PET/CT is more feasible for poorly-differentiated NENs (e.g., type 4). The typing algorithm of g-NENs is shown in *Figure 1*.

Typing-based treatment

The treatment strategies differ for different g-NEN types.

Type 1 gNET is caused by chronic (autoimmune) atrophic gastritis, achlorhydria, and hypergastrinemia. Gastroscopically it is manifested as mutiple small (<1–2 cm) polypoid lesions in gastric fundus/body. The prognosis is often good and metastasis is rarely seen, although recurrence is common (19,20). It has been well recognized that conservative treatment (endoscopic excision and follow-up) is better than surgery (21). Procedures of endoscopic resection remain contraversial: most authors suggest that watchful waiting is preferred for gastric lesions sized 1 cm or smaller and endoscopic resection [endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD)] should only be performed for ≥1 cm lesions. However, others also propose that all the visible small lesions should be removed with biopsy forceps; in particular, lesions sized ≥0.5 cm should be removed by endoscopic resection. No study has compared the effectiveness of proactive endoscopic treatment with that of selective endoscopic resection. In our opinion, lesions sized ≥0.5 cm should be treated by endoscopic resection; for lesions sized <0.5 cm (especially multiple lesions), endoscopic treatment is not feasible and endoscopic follow-up or medication is recommended.

For multiple small gastric lesions that are difficult to completely remove under endoscope or lesions that recur repeatedly after endoscopic resection, somatostatin analogs (SSAs) may be used because such drugs can lower serum gastrin, shrink tumors, and reduce relapse (22). Long-term use of SSA is required in patients with type 1 gNET because the disease may recur after the withdrawal of this drug (23). According to our experiences, SSA can be used for 1 year and then stopped for half year, thus achieving the long-term use of this drug at intervals.

Netazepide is a novel gastrin receptor antagonist. It was applied to treat eight patients with multiple type 1 g-NEN in a study (24); after 12 weeks of treatment, the number and size of the tumors decreased and the serum CgA returned normal, although the serum gastrin remained unchanged. This drug was well tolerated. A phase II clinical study of Netazepide further confirmed its efficacy. It may be a promising medical option for type 1 g-NEN patients.

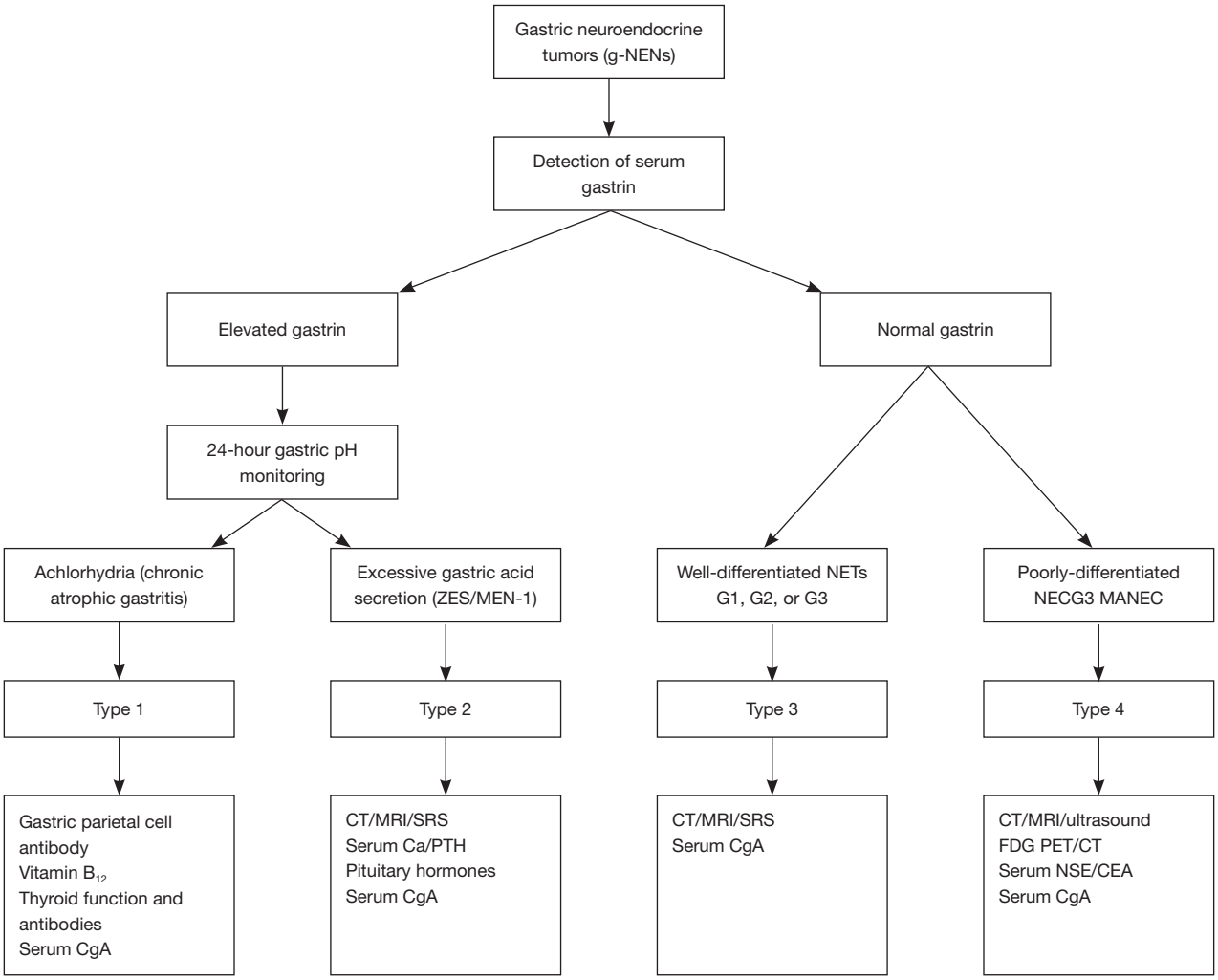

Figure 1 Diagnosis algorithm of gastric NET.

Type 2 g-NEN is mainly treated by surgery, during which both gastrinoma and metastatic lesions were resected. If the multiple metastases cannot be completely removed, SSA therapy may be applied; after the serum gastrin level decreases, the gastric polypoid lesions may also subside. Symptomatic treatment with PPI is often needed in patients with type 2 g-NEN.

For type 3 g-NEN patients with normal gastrin level, the treatment strategy during the localized phase is similar to that for gastric adenocarcinoma, i.e., partial or total gastrectomy plus lymph node dissection; if the tumor is ≤2 cm, endoscopic resection or wedge resection of the stomach may also be feasible. For type 3 g-NEN patients with distant metastasis, SSA is preferred to control the tumor (25,26), with the commonly used drugs including octreotide and lanreotide. These drugs have relatively mild toxicities and can be well tolerated by most patients. Regular ultrasound examinations are needed after long-term use of these drugs, in particular for gallbladder stones. Everolimus may be considered after SSA treatment failure. The RADIANT-4 study has demonstrated that everolimus can prolong the progression-free survival of patients with advanced gastrointestinal and pulmonary NETs (27). Notably, patients with severe accompanying diabetes or lung diseases should not use everolimus. Chemotherapy (preferably temozolomide alone or in combination with capecitabine) should be applied in type 3 g-NEN patients whose pathological diagnosis is "highly proliferative NET

(NET G3)".

In patients with poorly-differentiated gastric neuroendocrine carcinoma (type 4), partial or total gastrectomy plus regional lymph node dissection should be performed in patients with localized disease, in whom adjuvant chemotherapy should also be provided after surgery. However, distant metastasis had already occurred at the time of diagnosis in most type 4 patients, in whom the carcinoma is highly malignant and has already become unresectable. Thus, chemotherapy is preferred. EP (etoposide + platinol), the commonly used chemotherapy protocol for small cell lung cancer, has been used as the first-line treatment for type 4 g-NEN, with a response rate of 67% (28). The second-line treatment options include FOLFOX and FOLRIRI (29,30). Gastric mixed adenoneuroendocrine carcinoma (type 4) is extremely rare and cisplatin-based chemotherapy regimens are recommended (31). The role of SSA in type 4 g-NEN patients with positive octreotide scan results remain controversial.

Prognosis and follow-up

Type 1 g-NEN patients often have good prognosis, in whom metastasis is rarely seen, although the relapse of gastric lesion is common. The median time to relapse was 24 months. Thus, endoscopic follow-up is particularly important and should be performed every 6–12 months. Endoscopic resection is recommended for lesions sized >0.5 cm found during the follow-up visits. Meanwhile, serum gastrin and vitamin B_{12} levels should also be monitored. The prognosis is relatively poorer in type 2 patients, in whom the metastasis rate ranges 10–30% and the mortality rate is <10%. Gastroscopy should be performed on an annual basis for patients with type 2 g-NEN. In type 3 patients, the prognosis differs depending on the size and metastatic status of the tumor. Patients with tumors in their early stage that can be resected surgically or endoscopically may have good prognosis; however, more than half of the patients with type 3 g-NEN already have metastatic lesions at the time of diagnosis, among whom the tumor-related mortality rate range 25–30%. During the follow-up of type 3 patients with metastasis, the imaging items are same as for gastric adenocarcinoma. Type 4 patients have the poorest prognosis. Up to 80–100% of type 4 patients already have distant metastasis at the time of diagnosis. The survival is short. Assessment should be performed every 2–3 months during the treatment.

Conclusions

g-NENs are a group of heterogeneous tumors. Their treatment strategies and prognoses dramatically differ due to their types. The clinical typing of g-NENs should be a priority in clinical practice. Type 1 gNET is a recurrent gastric disease, and its preferred treatment is endoscopic resection and endoscopic follow-up. Not all type 1 g-NEN patients require SSA treatment. For patients with multiple and repeated recurrences, SSA may be considered. However, its high cost and potential toxicities hinders its application. Netazepide, a novel gastrin receptor antagonist, has shown promising efficacy in the treatment of type 1 g-NEN. The future research priorities include the molecular mechanisms of the recurrence of type 1 g-NEN and the R&D of safe and effective drugs (including TCM medicinals) for controlling the relapse of type 1 g-NEN.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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